restaging strategy,[4] with the goal of avoiding additional total mesorectal excision.

Defining the optimal primary endpoint is challenging because of variation in opinion between patients, clinicians, and regulatory agencies.[5] This challenge is even more relevant when the prognosis of cancer is good, as expected in good responders, and quality of life becomes a priority. Therefore, we proposed a composite endpoint including both oncological and non-oncological outcomes. We agree that absence of weighting in the composite endpoint makes interpretation difficult. However, we analysed each component separately as secondary endpoints to facilitate interpretation. Weighting each outcome of the composite endpoint does not necessarily facilitate interpretation, because weighting is prone to judgment calls. We also agree that GRECCAR2 was designed as a superiority trial and not powered to conclude for a non-inferiority hypothesis. Such a non-inferiority trial would require 1000 patients because of the low incidence of excellent responders.

We agree that the terminology per-protocol analysis, which is more familiar to clinicians, should be replaced by as-treated analysis,[6] which is more appropriate and corresponds with our statistical analyses. This complementary analysis should be seen as a secondary and non-randomised comparison, and did not change the results of the study.

We declare no competing interests.

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Pitfalls of the healthy vaccinee effect

We read with interest the Article by Helen Petousis-Harris and colleagues (Sept 30, 2017, p 1603),[1] which showed that the vaccine against outer membrane vesicle meningococcal B was 31% effective in reducing gonorrhoea among attendees of 11 clinics in New Zealand for patients with sexually transmitted infections. We disagree, however, with the authors' claims that their "findings provide experimental evidence that these vaccines could offer moderate cross-protection against [gonorrhoea]".

First, theirs was a non-experimental (observational) retrospective study in clinical research, in which efficacy claims require robust evidence from well conducted randomised controlled trials. Second, their findings are not robust, even by the standards of observational studies: use of patients with chlamydia as controls could have reduced the bias associated with differences in access to health care, but it probably did not lessen the effects of more pernicious confounders, such as the differences in lifestyle and behaviour between vaccinated and unvaccinated people.[2] Even among clinic attendees, chlamydia, which is often asymptomatic and only discovered on routine screening, might not be a suitable control condition for gonorrhoea, which is often associated with riskier sexual behaviour.[3] Gonorrhoea circulates in focused outbreaks among high-risk groups. Chlamydia is more egalitarian, affecting young people of all backgrounds.[4,5] We suspect that their control group was dominated by more health-conscious people with potentially higher vaccine uptake. If true, one would expect vaccines other than outer membrane vesicle meningococcal B vaccine to share the same protective effect. Our hypothesis can be tested in a sensitivity analysis by estimating the effectiveness of other vaccines, such as those against human papilloma virus or hepatitis B.

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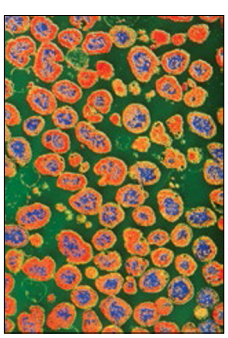
Authors' reply

In our Article,[1] we presented findings from a case-control study that showed a protective effect of a meningococcal vaccine against gonorrhoea infection. In their Correspondence, Salaheddin Mahmud and Christiaan Righolt argue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